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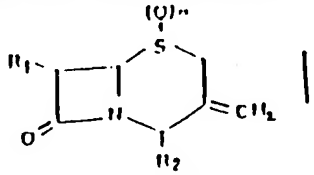
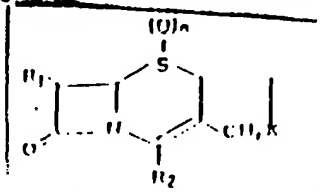
(54) Title : PROCESS FOR THE PREPARATION OF 3-EXOMETHYLENE CEPHALOSPORINS.

(57) Abstract : A new process for preparing 3-exomethylene cephalosporins of the formula :



Wherein
R_1 is amino or a protected amino group,
R_2 is a carboxy or a protected carboxy group and n is 0,1 or 2,

Which comprises reducing a 3-halomethyl-3-cephem derivative of the formula :



Wherein
R_1, R_2 and n are each as defined above and X is halogen atom, with active tin generated in $SnCl_2$-Al system in presence of organic solvents of the kind such as herein described.

(Ref. Nil). PRICE : RUPEES THIRTH ONLY

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FORM-3A

THE PATENTS ACT, 1970

COMPLETE

Specification

SECTION 10

The following Specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:—

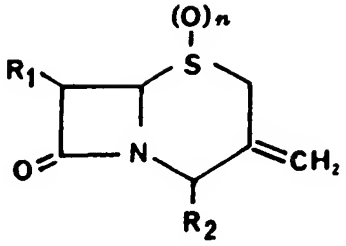
The invention relates to a new process for the preparation of 3-exomethylene cephalosporins.

These 3-exomethylenecepham compounds are useful as intermediates in the semisynthetic preparation of a variety of potent antimicrobial agents.

Several procedures are now available to produce 3-methylenecepham compounds. U.S. Patent No. 4,354,022 discloses a process for preparing 3-methylenecepham sulphides by reacting 3-halomethyl-3-cephem with a combination of activated Zinc metal and ammonium salt. However, of the 3-halomethyl-3-cephem compounds, only chloromethyl is exemplified in this reference. German patent no. 3,711,625 also describes the reduction procedure only for chloromethyl cephem compounds. In Chem. Pharm. Bull. 36(2) 582-591 (1988) the preparation of 7-amino-3-methylene cepham-4-carboxylic acid is given by reduction of the corresponding 3-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl-3-cephem derivative with zinc either in acidic or in anhydrous neutral conditions. In European Patent Appl. 132, 394, the preparation of 3-methylene-1-oxocephem compounds is given by reaction of the corresponding 3-acetoxymethyl cephem compounds with activated zinc and ammonium chloride.

In accordance with the present invention there is provided a new process using active tin generated in $SnCl_2$-Al system to achieve 3-exomethylene cephalosporin compounds of high purity and in good yields. The side product 3-methyl-3-cephem compound is formed in minor quantity in the method described in the present invention.

According to the present invention, 3-exomethylene cephalosporins of the formula :



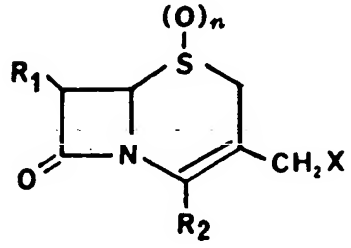
I

Wherein

R_1 is amino or a protected amino group,

R_2 is a carboxy or a protected carboxy group and

n is 0, 1 or 2, can be prepared by reducing a compound of the formula



II

Wherein

R_1, R_2 and n are each as defined above and

X is halogen, by the use of active zero-valent tin generated in $SnCl_2$-Al system, in a solvent, at a temperature of about 5°C to about 60°C.

Suitable "protected amino group" may include an amino group substituted with a suitable protective group which is conventionally used in Cephalosporin and Penicillin compounds as a protective group of the amino group at their 7th or 6th position, and suitable 'protected amino group' may include acylamino, phenyl (lower) alkylamino. (cyclo) alkylamino.

Suitable 'acylamino' groups include aliphatic, aromatic and heterocyclic acylamino groups, the acyl group being for example formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl, methoxy carboxyl, ethoxycarbonyl, t-butoxycarbonyl, benzoyl, toluoyl, naphthoyl, phenylacetyl, phenylpropionyl, phenoxycarbonyl, phenoxyacetyl, thienylacetyl.

Suitable 'protected carboxy group' may include a carboxy group substituted with a conventional protective group which is conventionally used in cephalosporin and penicillin compounds as the carboxy protective group of the carboxy group at their 4th and 3rd position, for example, esterified carboxy group. Suitable examples of such protected carboxy groups include esters such as methyl ester, ethyl ester, propyl ester, butyl ester, benzyl ester, 4-nitrobenzyl ester, 2,2,2-trichloroethyl ester, diphenylmethyl ester, 4-methoxybenzyl ester.

In this specification, halogen may include chlorine, bromine and iodine.

Preferred compounds of formula I which can be made by the present invention are 3-methylene cepham and most preferably the 3-methylene-1-oxocepham and 3-methylene-1,1-dioxocepham compounds.

The reduction of compound II for the preparation of the compound I of the invention is accomplished with stannous chlorid dihydrate and aluminium powder.

Numb r of solvents can b mployed as suitable reaction solvent in the proc ss. The solvent select d is pr f rrably one in which the 3-halomethyl cephem substrate is substantially soluble. Solvents most commonly used include N,N,-dimethyl formamide, acetonitrile, tetrahydrofuran, water, dioxane.

The reaction conditions are not very critical. The reaction temperature range optimal for the reaction according to the invention may vary depending on the starting material, solvent and other factors. Generally, however the range of about 5°C to 60°C is suitable. The reaction time may vary widely, but is usually between 1-4 hrs. The product can be purified, removing any 3-methyl-3-cephem cr ether impurities which might be present, by standard usual techniques including crystallization from solvents such as methanol, isopropanol or acetone.

The starting 3-halomethyl-3-cepham derivatives are known compounds and may be prepared by the appropriate known methods. See, for example Japanese patent no. 76087/1975, Eur. Pat. Appl. 34,394 and Belgian patent no. 755, 256.

As mentioned earlier, the 3-exomethylene cephams produced by the present process of this invention are useful as intermediates in the synthesis of cephalosporins having antibacterial activity. The 3-exomethylene cepham-1-oxides are paticularly valuable in the synthesis of 3-hydroxy-cephalosporins, which may be converted readily to 3-halocephalosporins.

The following examples are given for the purpose of illustrating the present invention.

EXAMPLE-1

DIPHENYLMETHYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-1-OXIDE-4-CARBOXYLATE

To a stirred solution of 5 g of diphenylmethyl 7-phenylacetamido-3-bromomethyl-3-cephem-1-oxide-4-carboxylate in 130 ml tetrahydrofuran and 50 ml water were added 5g of stannous chloride dihydrate and 1.53 g aluminium powder at 10-15°C. The reaction progress was monitored by TLC. After the completion of the reaction, 100 ml ethyl acetate was added and organic layer was separated. Removal of the solvent afforded 4.30 g of the product that was recrystallised from isopropyl alcohol. According to quantitative HPLC-assay, the product contained 95% of the title compound. The isolated yield of the title 3-exomethylene was 87%. PMR (DMSO-d_6) δ : 3.45, 3.72 (2H, ABq, J=15Hz, C-2), 3.46 (2H, d, J=1.5Hz,-CH_2CO), 4.78 (1H, d, J=5Hz, C-6), 5.20, 5.32 (2H, 2s, 3-exomethylene), 5.41(1H, dd, J=5Hz, 10Hz, C-7), 5.58 (1H, s, C-4), 6.54(1H, s, diphenylmethylmethine), 7.08 (15H, m, aromatic) and 7.78 (1H, d, J=10Hz, -NH).

EXAMPLE-2

4-METHOXYBENZYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-1-OXIDE-4-CARBOXYLATE

When proceeding according to the method described in example 1 and using 4.60 g of 4-methoxybenzyl 7-phenylacetamido-3-bromomethyl-3-cephem-1-oxide-4-carboxylate, 3.30g of 4-methoxybenzyl 7-B-phenylacetamido-3-exomethylenecepham-1-oxide-4-carboxylate (85% of theory) were obtained. HPLC analysis confirmed the product to be composed of 97% pure 3-exomethylenecepham.

EXAMPLE-3

TERT. BUTYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-1-OXIDE-4-CARBOXYLATE

To a solution of tert. butyl 7-β-phenylacetamido-3-bromomethyl-3-cephem-1-oxide-4-carboxylate (5 g) in 100 ml of tetrahydrofuran and 40 ml water was added 6.10 g stannous chloride dihydrate followed by 1.87 g aluminium powder at 20-25°C. The whole was stirred at 30-35°C for 1 hr and 200 ml ethyl acetate added. After filteration, organic layer was washed and concentrated under reduced pressure until thick paste was formed. Diethyl ether (200 ml) was added slowly and mixture stirred at 0-5°C for 1 hr. The precipitate was filtered off, washed with 20ml ether and dried, giving 3.68 g of the title compound as white solid. Yield was 88%.

PMR (DMSO-d_6) δ : 1.35 (9H, s, tert. butyl), 3.35 (2H, d, J=2Hz CH_2CO), 3,.45, 3.7 (2H, ABq, J=16Hz, C-2), 4.69 (1H, d, J=5Hz, C-6), 4.83, 5.05 (2H, 2s, 3-exomethylene), 5.35 (1H, s, C-4), 5.3 (1H, dd, J=5Hz, 8Hz, C-7), 6.91 (5H, s, aromatic) and 7.65 (1H, d, J=8Hz, -NH)

EXAMPLE-4

2,2,2-TRICHLOROETHYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-1-OXIDE-4-CARBOXYLATE

2g Trichloro 7-β-phenylacetamido-3-bromomethyl-3-cephem-1-oxide-4-carboxylate dissolved in a mixture of tetrahydrofuran (14ml) and water (6 ml) was treated with stannous chloride dihydrate (2g) and aluminimum powder (0.64g) at 30-35°C. After stirring for 30 min at 25-30°C, 80 ml ethylacetate and 20 ml of 3% hydrochloric acid solution was added and the layers were separated. The ethyl acetate solution was washed twice with 10% sodium chloride solution (20ml) dried over sodium sulphate and concentrated to a thick paste. Diethyl ether (40 ml) was added and

resulting precipitate was filtered and purified from iso-propyl alcohol to provide 1.54 g of the title 3-exomethylenecepham with a purity of 96% (HPLC). The yield was 89%.

PMR (DMSO-d_6) δ : 3.48 (2H, d, J=2Hz, CH_2CO), 3.55, 3.84 (2H, ABq., J=18Hz, C-2), 4.74 (3H, bs, CH_2CCl_3 and C-6), 5.2, 5.32 (2H, 2s, exomethylene), 5.38 (1H, dd, J=5Hz, 8Hz, C-7), 5.55 (1H, s, C-4), 6.72 (5H, s, aromatic) and 7.80 (1H, d, J= 8Hz,-NH).

EXAMPLE-5

DIPHENYLMETHYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-4-CARBOXYLATE

To a solution of diphenylmethyl 7-β-phenylacetamido-3-bromo-methyl-3-cephem-4-carboxylate (1 g) in a mixture of 10 ml tetrahydrofuran and 4 ml water was addedd stannous chloride dihydrate (1.2 g) followed by aluminium powder (0.5g) and the reaction mass was stirred at 60-65°C for 1 hr. Ethyl acetate (40 ml) was added and organic layer separated, washed twice with 10 ml water. After drying with sodium sulphate, the solvent was removed under reduced pressure and the residue was crystallized with ethylacetate/di-isopropyl ether to afford 690 mg (80%) of the desired exomethylene product with 82% purity.

EXAMPLE-6

DIPHENYLMETHYL 7-β-PHENYLACETAMIDO-3-EXOMETHYLENECEPHAM-4-CARBOXYLATE

To a solution of 500 mg of diphenyl 7-β-phenylacetamido-3-bromomethyl-3-cephem-4-carboxylate in 15 ml of acetonitrile and 1 ml water was added stannous chloride dihydrate (0.6g) and aluminium powder (0.25 g) and the reaction mixture stirred at 30-35°C for 30 min. After usual work up and purification from ethyl acetate/di-iso-propyl ether, 325 mg of exomethylene

cepham was obtained (yield 75.4%). According to quantitative HPLC-assay the purity was 95.8%.

PMR ($CDCl_3$) δ : 2.90, 3.30 (2H, ABq, J=16Hz, C-2), 3.39 (2H, s, CH_2CO), 4.88, 4.92, 4.98 (3H, 3s, exomethylene and C-4), 5.05 (1H, d, J=5Hz, C-6), 5.35 (1H, dd, J=5Hz, 9Hz, C-7), 5.88 (1H, d, J=9Hz, NH), 6.50 (1H, s, ϕ_2CH) and 6.9-7.2 (15H, aromatic)

EXAMPLE-7

DIPHENYLMETHYL 7-β-AMINO-3-EXOMETHYLENE-4-CARBOXYLATE HYDROCHLORIDE

To solution of cyclohexene (0.97 g) and pyridine (1.84g) in 45 ml of dichloromethane was added diphenylmethyl 7-phenylacetamido-3-exomethylenecepham-1-oxide-4-carboxylate (prepared from corresponding 3-halomethyl derivative as described in example 1) and the mixture cooled to -45°C. Phosphorus pentachloride (4.86 g) was then introduced causing a rise in temperature to -40°C. After stirring at -40°C for 30 minutes, the temperature was raised to about 10°C and mixture stirred further for 1 hr. Subsequently, 18.7 ml of methanol was added and mixture was stirred for 1 hr. To the resulting solution was added cold water (2 ml). After removing the solvent in vacuo, the residue was triturated with water (4 ml) and diethylether (30 ml). Resulting precipitate was collected by filtration, washed with water (10 ml), diethyl ether (10ml) and dried to afford 1.72 g (70%) of the title compound of 98% purity by HPLC analysis.

PMR (DMSO-d_6) δ : 3.25, 3.50 (2H, ABq. J=18H, C-2), 4.68 (1H, d, J=5Hz, C-6), 5.02 (1H, d,J=5Hz,C-7), 5.19 (2H, s, 3-exomethylene), 5.20 (1H, s, C-4), 6.55 (1H, s, benzhydryl H) and 6.97 (10H, bs, aromatic).

we claim

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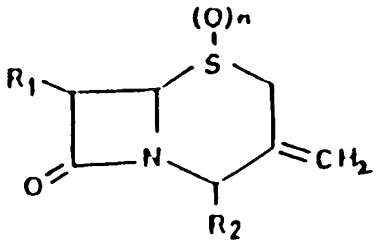
1. A new process for preparing 3-exomethylene cephalosporins of the formula :

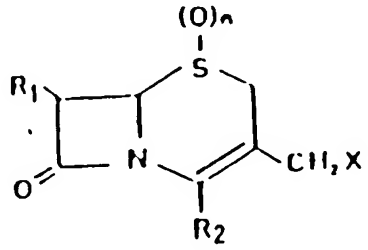


Wherein

R_1 is amino or a protected amino group,

R_2 is a carboxy or a protected carboxy group and n is 0, 1 or 2,

Which comprises reducing a 3-halomethyl-3-cephem derivative of the formula



Wherein

R_1, R_2 and n are each as defined above and
X is halogen atom, with active tin generated in $SnCl_2$-Al system in presence of organic solvents of the kind such as herein described .

2. The Process according to claim 1, wherein said organic solvents are selected from tetrahydrofuran or acetonitrile or mixture thereof capable of dissolving the 3-halomethylcephem derivatives and water.

3. The process according to claim 2, in which the reaction is carried out at a temperature of about 5C to 60C.

4. A new process for preparing 3-exomethylenecepham compounds of the formula I substantially as herein described with reference o foregoing examples.

Dated this 10th day of May, 1991.

For RANBAXY LABORATORIES LTD.

SECRETARY

APPLICANT